Penn Frontotemporal
Degeneration Center

# Adjusting plasma p-tau217 levels for kidney function to improve association with amyloid and tau pathology

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ADNI Alzheimer's Disease Neuroimaging Initiative

Penn University of Pennsylvania | Alzheimer's Disease Research Center

## Background

- Plasma phosphorylated tau 217 (**p-tau$_{217}$**) measured by Fujirebio Lumipulse (RUO) shows excellent performance to detect abnormal β-amyloid (**Aβ**), indicative of Alzheimer's disease (**AD**)
- Comorbidities may confound AD blood biomarker levels, thereby affecting performance:
  - Kidney function alters blood p-tau$_{217}$ levels independently of AD pathology: chronic kidney disease (**CKD**) (*i.e.*, low estimated glomerular filtration rate [**eGFR]**) can lead to false positives by p-tau$_{217}$
  - Conversely, higher body mass index (**BMI**) is associated with lower blood p-tau$_{217}$
- It is unclear whether strategies accounting for these conditions improve blood biomarker accuracy and interpretation
- Here we evaluate whether linear adjustments can improve blood biomarker associations with AD pathology
- **Study Goals**:
  1. In Aβ PET negative (Aβ-) cases, we model plasma p-tau$_{217}$ adjusted for eGFR and BMI
  2. Compute adjusted p-tau$_{217}$ values in all participants
  3. Test if adjusted p-tau$_{217}$ strengthens correlations with Aβ and tau PET, compared to unadjusted (raw) p-tau$_{217}$
  4. Test if p-tau$_{217}$ adjustment improves biomarker classification

## Methods & Participants

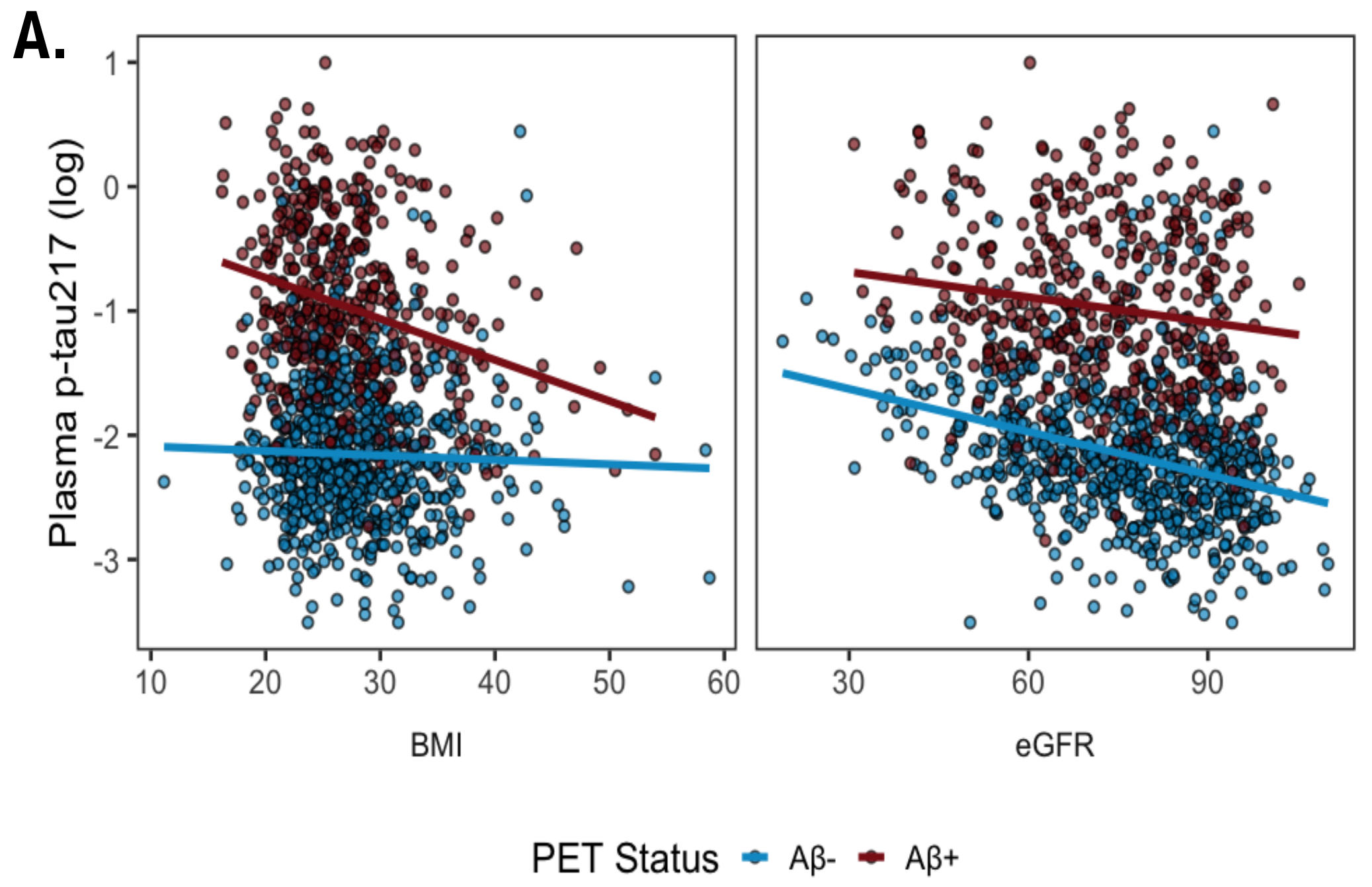
| | ADNI | ADNI Aβ- | ADNI Aβ+ | p |
|---|---|---|---|---|
| n | 17 | 702 | 448 | |
| Aβ PET Centiloid | -- | 2.5 [-4.0, 8.0] | 74.0 [46.0, 102.2] | <0.001 |
| Global TauMax | 23.6 [0.2, 39.2] | 0.0 [0.0, 0.0] | 0.5 [0.0, 9.1] | <0.001 |
| Tau PET SUVR | 1.3 [1.2, 2.0] | 1.2 [1.1, 1.2] | 1.3 [1.2, 1.6] | <0.001 |
| Cognitive Status = MCI (%) | 12 (70.6%) | 225 (32.1%) | 279 (62.3%) | <0.001 |
| Age at Plasma (years) | 70.8 [66.0, 73.7] | 71.6 [65.6, 77.0] | 75.6 [70.3, 80.5] | <0.001 |
| eGFR | 79.2 [67.4, 90.6] | 77.9 [65.3, 89.5] | 73.3 [61.9, 85.0] | <0.001 |
| Body Mass Index (BMI) | 26.2 [23.5, 31.0] | 27.1 [24.0, 30.8] | 26.1 [23.4, 29.6] | 0.024 |
| Years from plasma to eGFR | 0.2 [0.1, 0.3] | 0.1 [0.0, 0.2] | 0.1 [0.0, 0.2] | 0.109 |
| Sex = Male (%) | 7 (41.2%) | 302 (43.0%) | 195 (43.5%) | 0.972 |
| Self-reported Race (%) | | | | <0.001 |
| White | 9 (52.9%) | 457 (66.2%) | 354 (79.2%) | |
| Black | 7 (41.2%) | 148 (21.4%) | 69 (15.4%) | |
| Other/Unknown | 1 (5.9%) | 85 (12.3%) | 24 (5.4%) | |
| Ethnicity = Hispanic (%) | 0 | 89 (12.7%) | 28 (6.3%) | 0.001 |
| APOE = ≥1 ε4 allele(s) (%) | 10 (62.5%) | 154 (23.4%) | 286 (66.8%) | <0.001 |

**Table 1. ADNI sample characteristics.** Median [interquartile range] and Kruskal Wallis p-values are reported for continuous variables; count (Percentage) and chi-square p-values for categorical.

- Participants were selected from the Alzheimer's Disease Neuroimaging Initiative (**ADNI**) (n= 1,167)
  - Inclusion criteria: measurements for plasma p-tau$_{217,}$ **eGFR calculated from creatinine**, body mass index (**BMI**), and either Aβ or tau PET
  - Exclude eGFR measurements >2years from plasma
  - Cognition was normal (n=651) or mild cognitive impairment (**MCI**; n=516)
  - Missing data: Aβ PET (n=17), Tau PET SUVR (n=221), TauMax (n=506), Race (n=13), Ethnicity (n=4), APOE ε4 (n=67)
- Aβ PET Status: Centiloids≥20 = Aβ+; Centiloids<20 = Aβ-
- Fujirebio Lumipulse measured plasma p-tau$_{217}$ at Penn
- Adjusted p-tau$_{217}$ based on model in Aβ-:
  plasma p-tau$_{217}$ (log) ~ eGFR + BMI (Figure 1)

## Results: Computing eGFR+BMI-adjusted plasma p-tau$_{217}$

A.



B.

| Plasma p-tau217 in PET Aβ- | β | 95%CI | p |
|---|---|---|---|
| **eGFR** | -0.012 | -0.014 – -0.01 | <0.0001 |
| **Body Mass Index (BMI)** | -0.010 | -0.016 – -0.003 | 0.0075 |

C.

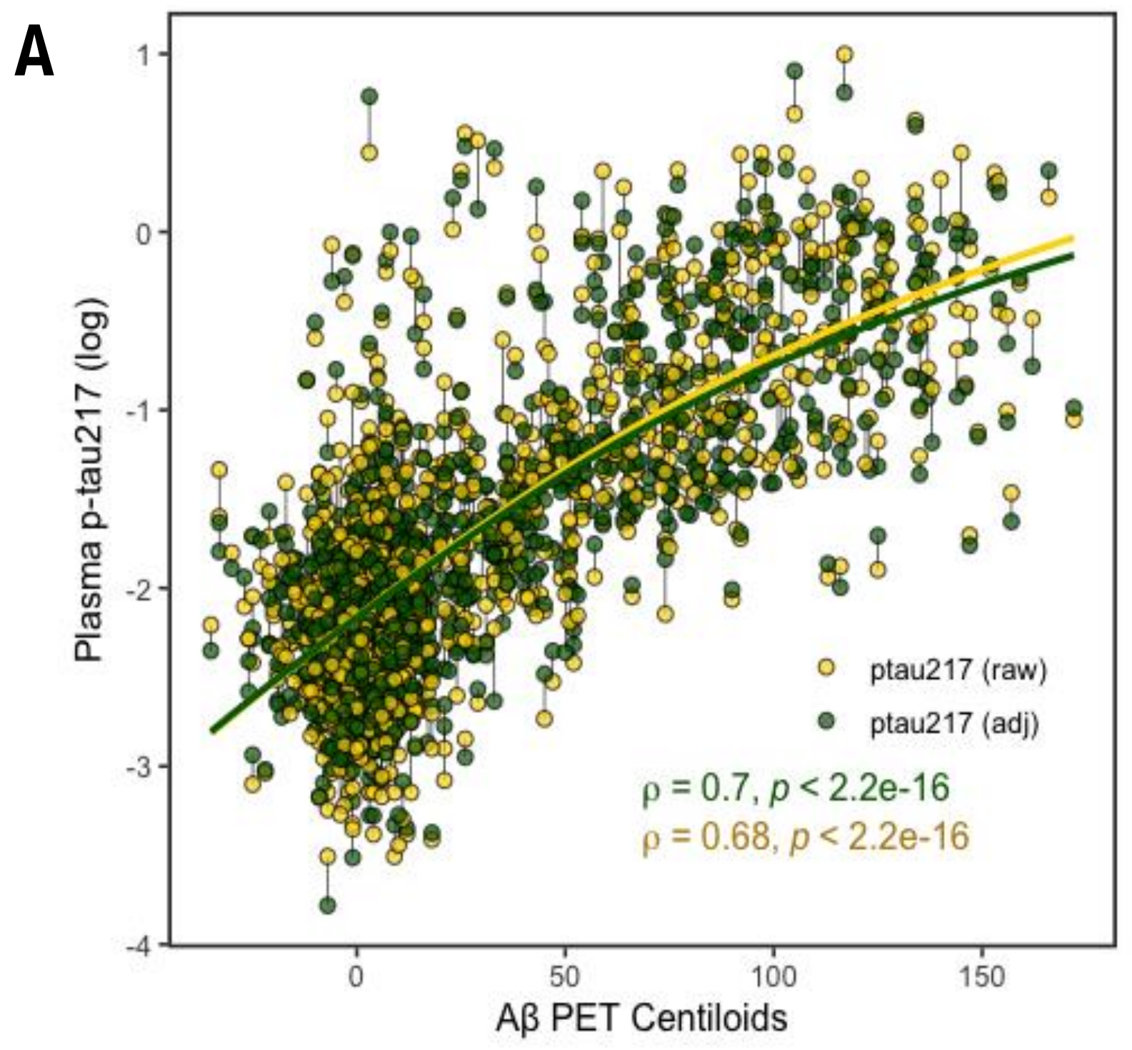
| Plasma p-tau217 in all ADNI | β | 95%CI | p |
|---|---|---|---|
| **eGFR** | -0.011 | -0.014 – -0.008 | <0.0001 |
| **Body Mass Index (BMI)** | -0.011 | -0.019 – -0.003 | 0.0070 |
| Age at Plasma (years) | 0.004 | -0.002 – 0.01 | 0.1675 |
| **Sex = Male** | 0.147 | 0.066 – 0.228 | 0.0004 |
| Race = Black | -0.102 | -0.213 – 0.009 | 0.0720 |
| RaceOther/Unknown | -0.032 | -0.197 – 0.133 | 0.7021 |
| **Aβ PET SUVR** (log) | 2.100 | 1.835 – 2.365 | <0.0001 |
| **Tau PET temporal SUVR** (log) | 1.641 | 1.306 – 1.976 | <0.0001 |

**Figure 1. Plasma p-tau$_{217}$ associations with eGFR and BMI.** (**A.**) Scatterplots and least squares regression lines of plasma p-tau$_{217}$ log-transformed by BMI and eGFR. Color indicates Aβ PET status. (**B.**) Linear model of p-tau$_{217}$(log) as a function of BMI and eGFR in PET Aβ- cases. This model was applied to the full sample to calculate adjusted values. (**C.**) Linear model of p-tau$_{217}$(log) as a function of BMI, eGFR, and Aβ and tau pathologies in all cases.

- Computed adjusted values in all participants based on model (Figure 1B)

## Results: Correlations with PET Aβ and tau

A



- Zou's (2007) confidence interval method compared p-tau$_{217}$ adjusted vs. raw, with significantly stronger correlations for Aβ Centiloids and TauMaX, but not temporal tau SUVR:
- Aβ Centiloids: Difference = 0.017, 95%CI= 0.001 – 0.033
- TauMaX: Difference = 0.070, 95%CI= 0.047 – 0.096
- Tau Temporal SUVR: Difference = 0.013, 95%CI= -0.007 – 0.034

B.

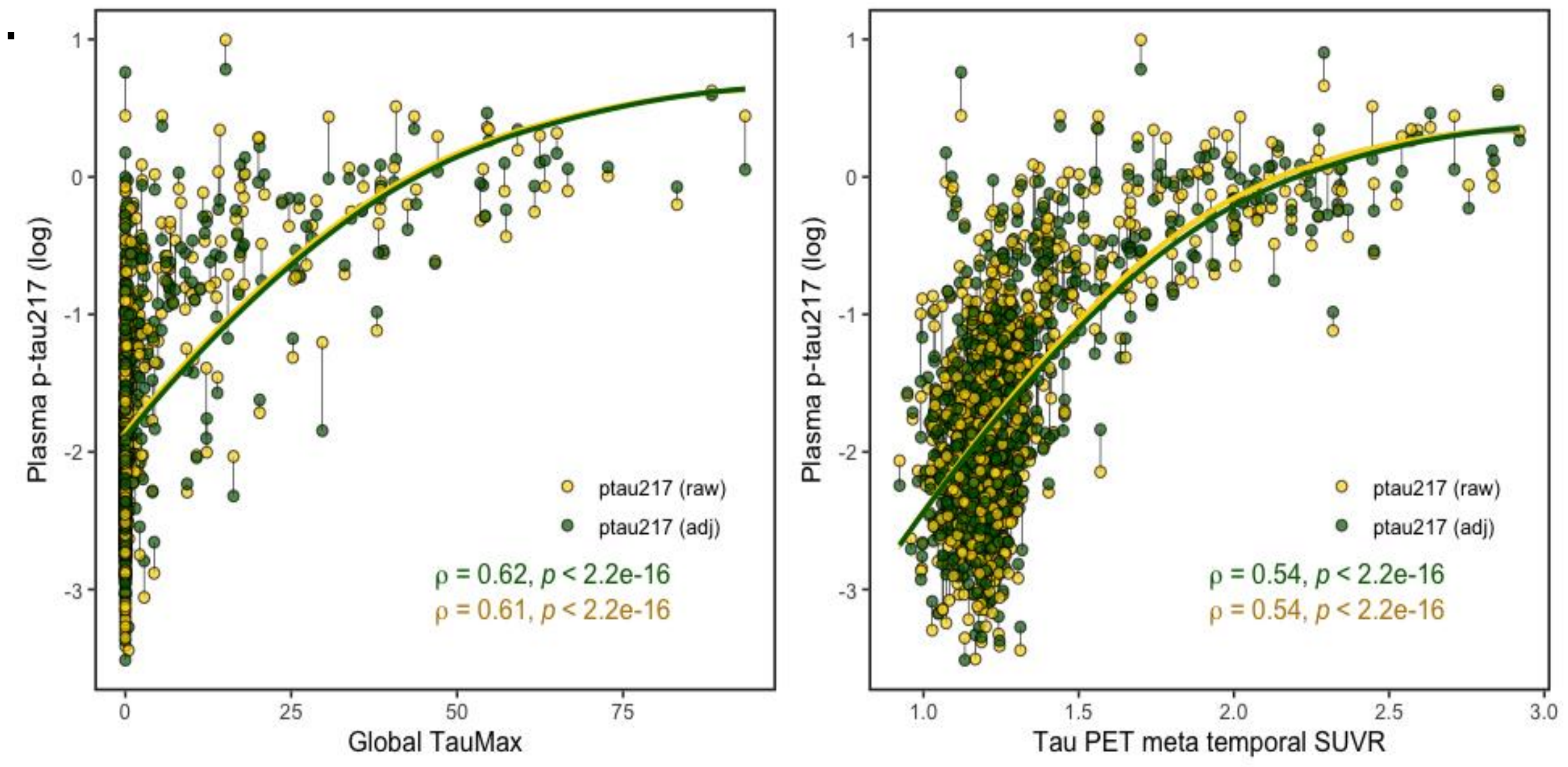
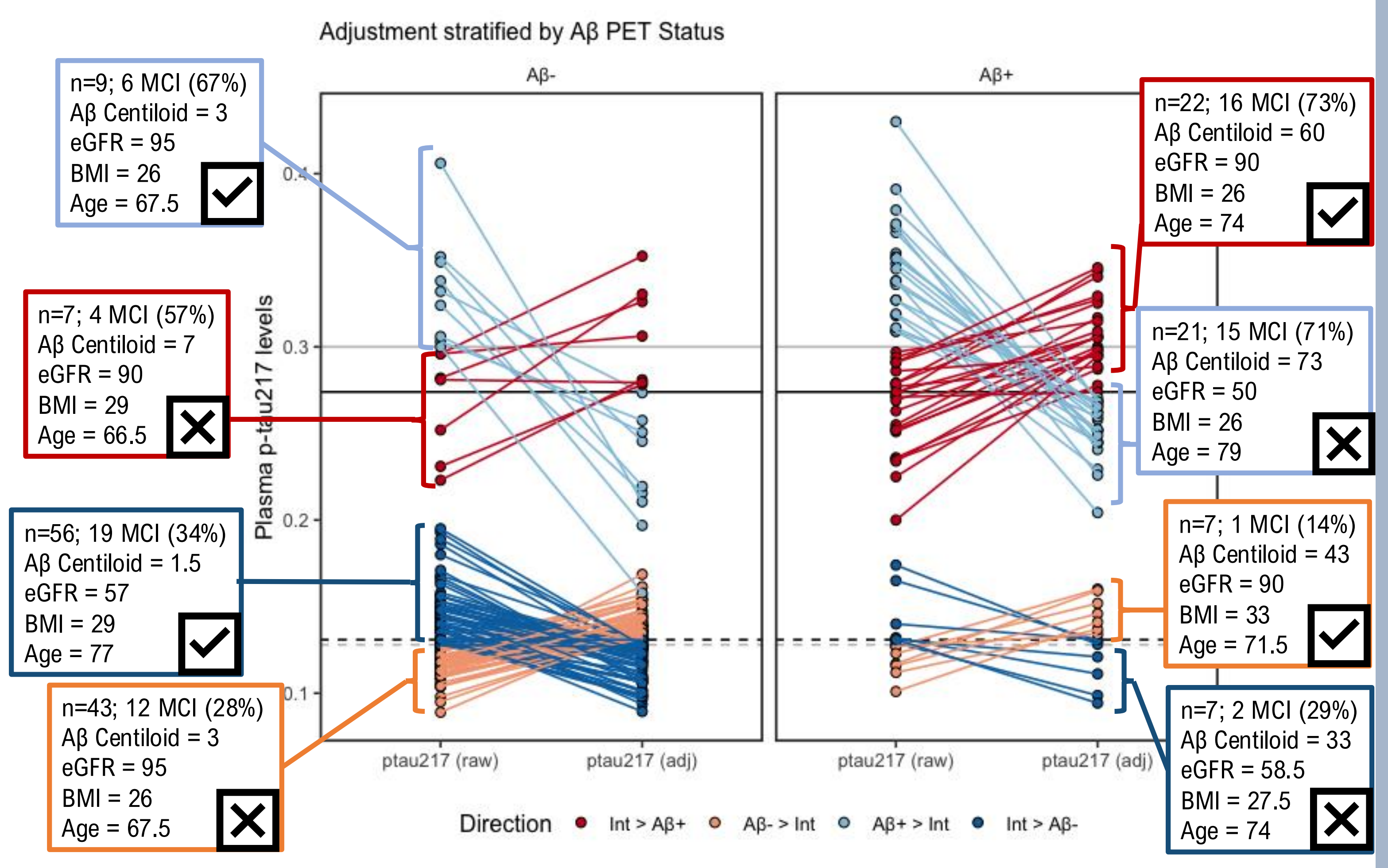


**Figure 2. Scatterplots comparing Spearman correlations with AD pathology.** (**A.**) Aβ PET Centiloids correlations with plasma p-tau$_{217}$ log-transformed adjusted ([adj] green) vs. raw (yellow). (**B.**) Tau PET TauMaX and meta temporal SUVR score for Flortaucipir) correlations with plasma p-tau$_{217}$ adjusting (adj; green) vs. raw (yellow). Spearman's rho and p-value are reported.

## Results: AD classification using eGFR+BMI-adjusted plasma p-tau$_{217}$



n=9; 6 MCI (67%)
Aβ Centiloid = 3
eGFR = 95
BMI = 26
Age = 67.5 ✓

n=7; 4 MCI (57%)
Aβ Centiloid = 7
eGFR = 90
BMI = 29
Age = 66.5 ☒

n=56; 19 MCI (34%)
Aβ Centiloid = 1.5
eGFR = 57
BMI = 29
Age = 77 ✓

n=43; 12 MCI (28%)
Aβ Centiloid = 3
eGFR = 95
BMI = 26
Age = 67.5 ☒

n=22; 16 MCI (73%)
Aβ Centiloid = 60
eGFR = 90
BMI = 26
Age = 74 ✓

n=21; 15 MCI (71%)
Aβ Centiloid = 73
eGFR = 50
BMI = 26
Age = 79 ☒

n=7; 1 MCI (14%)
Aβ Centiloid = 43
eGFR = 90
BMI = 33
Age = 71.5 ✓

n=7; 2 MCI (29%)
Aβ Centiloid = 33
eGFR = 58.5
BMI = 27.5
Age = 74 ☒

**Figure 3. Changes in biomarker status, stratified by PET Aβ status.** Panels stratify by PET Status, color indicates pairwise increase (red = Intermediate to Aβ+, coral = Aβ- to Intermediate) or decrease (light blue = Aβ+ to Intermediate, dark blue = Intermediate to Aβ-) of p-tau$_{217}$ adjusted (adj) compared to raw. Lines indicate 95% specificity (solid) and 95% sensitivity cutpoints (dotted) for raw (grey) and adjusted (black) p-tau$_{217}$. Annotations indicate number and mean Aβ Centiloid, eGFR, BMI, and age for each group.

## Conclusions & Future Directions

- ✓ eGFR and BMI were significantly associated with plasma p-tau$_{217}$ concentrations, even after for controlling for age, Aβ and tau pathologies (Figure 1B and 1C)
- ✓ Linear adjustments of plasma p-tau$_{217}$ showed incremental improvement compared to raw values:
  - ✓ Spearman correlations with Aβ PET (Figure 2A) and TauMaX (Figure 2B) were slightly higher for adjusted compared to raw plasma p-tau$_{217}$
  - ✓ Receiver operating curve (ROC) area under the curve was slightly higher for adjusted (AUC=0.91) than raw p-tau$_{217}$ (AUC=0.90)
  - ✓ Overall, 16 of 1150 cases had improved classification using adjustment: 1 Aβ+ case and 15 Aβ- cases (Figure 3)
- Future work should evaluate in populations with more severe morbidities, and test alternative strategies such as eGFR calculated by Cystatin C or non-linear adjustment

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